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Brief Clinical Report

Smith-Lemli-Opitz Syndrome: Thirty-Year Follow-Up of "S" of "RSH" Syndrome

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We have reassessed patient "S," one of the first 3 individuals recognized to have Smith-Lemli-Opitz (or RSH) syndrome, at age 34 years, and we describe his physical, developmental, and behavioral manifestations. This reassessment provides formal evidence that this individual has the cholesterol biosynthetic defect which is thought to be the cause of Smith-Lemli-Opitz syndrome. Dietary manipulation appears to have had a beneficial effect on the patient's behavior and suggests that even in adults with this condition, dietary cholesterol supplementation may be indicated. Am. J. Med. Genet. 68:260–262, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Smith-Lemli-Opitz syndrome; cholesterol; long-term follow-up

INTRODUCTION

The first patients with Smith-Lemli-Opitz syndrome were described over three decades ago [Smith et al., 1964]. This disorder was dubbed RSH syndrome by Opitz et al. [1969] and Opitz [1994], using the initials of the surnames of the first recognized affected individuals.

The pathogenesis of this disorder remained unknown until the recent demonstration that individuals with Smith-Lemli-Opitz syndrome have an abnormality of cholesterol biosynthesis [Irons et al., 1993, 1994; Tint et al., 1994]. Deficient 7-dehydrocholesterol C-7 reductase activity [Shefer et al., 1995; Honda et al., 1995] results in reduced plasma and tissue cholesterol levels and elevated 7-dehydrocholesterol concentrations. In turn, it is postulated that all of the structural and functional abnormalities of this syndrome are a consequence of this enzymopathy [Opitz, 1994].

Recently we had the opportunity to reassess patient "S," one of the three original patients described by Smith et al. [1964], and we present a 30-year follow-up of this individual, along with evidence that one of the original Smith-Lemli-Opitz syndrome patients does, indeed, have the biosynthetic defect thought to be the basis of this disorder. Finally, this follow-up has provided an opportunity to informally assess the effects of dietary cholesterol supplementation [Irons et al., 1994, 1995; Xu et al., 1995] in one of the oldest known patients with this syndrome.

CLINICAL REPORT

Medical and developmental history of "S" to age 18 months was published in Smith et al. [1964]. He had virtually all of the usual phenotypic characteristics of Smith-Lemli-Opitz syndrome, including abnormalities of growth, neurologic function, genital form, craniofacial features, and dermatoglyphic patterns [Smith et al., 1964].

We reassessed him at age 33 9/12 years. From late infancy until recently he was cared for in residential institutions. During his adult years much of his time at these institutions was spent heavily medicated and in restraints because of otherwise uncontrollable behavior. More recently he has been fostered in a group home farm, with some improvement in his difficult behavior.

Adult behavior is principally characterized by intermittent explosive episodes, mostly with destruction of objects, but occasionally resulting in injury to self or others. At the time of initial placement at the group home farm, these outbursts occurred 15–30 times a month, but more recently have diminished to about 3–4 such episodes a month. Often a precipitant (e.g., unwillingness to conform to other behavioral expectations) can be identified.

General health has been excellent. He has a seizure disorder which is under good pharmacologic control.

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Medications include only those prescribed in an effort to control his seizures and his behaviors, including propranolol, lithium, haloperidol, benztropine mesylate, and diphenylhydantoin.

He is severely mentally retarded (estimated developmental quotient of about 20 and estimated development ranging from 2 years for cognitive skills to about 4 years for motor performance). He has 10–15 functional words but mostly makes his desires known through gestures and grunting. He does have some sense of empathy and can understand sadness in others. Favorite activities include watching automobiles drive by, television, riding his three-wheel bicycle, and playing with animals.

Physical examination was interrupted periodically by vocal outbursts and episodes of lunging at the examiner. However, these threat attacks were not followed by any physical effort to cause harm. Height is 170.0 cm, weight 61 kg, and occipitofrontal circumference 51.7 cm. He is mildly microcephalic with a markedly flat occiput. He also has prominent supraorbital ridges, very bushy eyebrows, marked ptosis, epicanthic folds, heterochromia iridis (blue-green on right and light brown on left), mild hypoplasia of the malar region, broad nose, an open bite, anomalous wear of the incisors, and a submucosal cleft palate with a V-shaped indentation of the bony palate and marked tenting of the soft palate on elevation. He has a pectus excavatum and a left accessory nipple. There is generalized brachydactyly, shortness of the proximal phalanges of the fifth fingers, and mild soft tissue syndactyly of left fingers 3 and 4. He has considerable hyperextensibility of the proximal interphalangeal joints. Fingertip dermatoglyphic patterns are all whorls. Feet show a pes cavus configuration unloaded, but a markedly hypermobile arch resulting in pes planus when loaded. He has marked soft-tissue syndactyly bilaterally of toes 2 and 3. Genital examination was not allowed but, by history, he has an unrepaired hypospadias and chordee. Craniofacial appearance, when first reported and currently, is shown in Figure 1.

Plasma sterols were: cholesterol, 65 mg/dl; 7-dehydrocholesterol, 30 mg/dl; and 8-dehydrocholesterol, 12 mg/dl. These levels are diagnostic of individuals with Smith-Lemli-Opitz syndrome type I [Tint et al., 1995].

Diet analysis showed that 22% of calories were obtained from fat, and average daily cholesterol intake was only 69 mg. Because of the possible benefit of dietary supplementation with cholesterol [Irons et al., 1994, 1995], diet modification was recommended to include daily incorporation of three whole eggs and supplementation of whole milk, together calculated to increase daily dietary cholesterol intake by approximately 700 mg. Two months following initiation of this diet, caregivers described the patient as "calmer, happier, and more verbal." Repeat assessment of plasma sterols following diet initiation showed: cholesterol, 70 mg/dl; 7-dehydrocholesterol, 39 mg/dl; and 8-dehydrocholesterol, 19 mg/dl.

DISCUSSION

This reassessment provides confirmation of the potential for long-term survival without apparent life-threatening sequelae in individuals with Smith-Lemli-Opitz syndrome. Phenotypic manifestations persist and, unlike other observers [deDie-Smulders and Fryns, 1992], we were struck by this persistence of all of the diagnostically relevant abnormalities 34 years after birth.

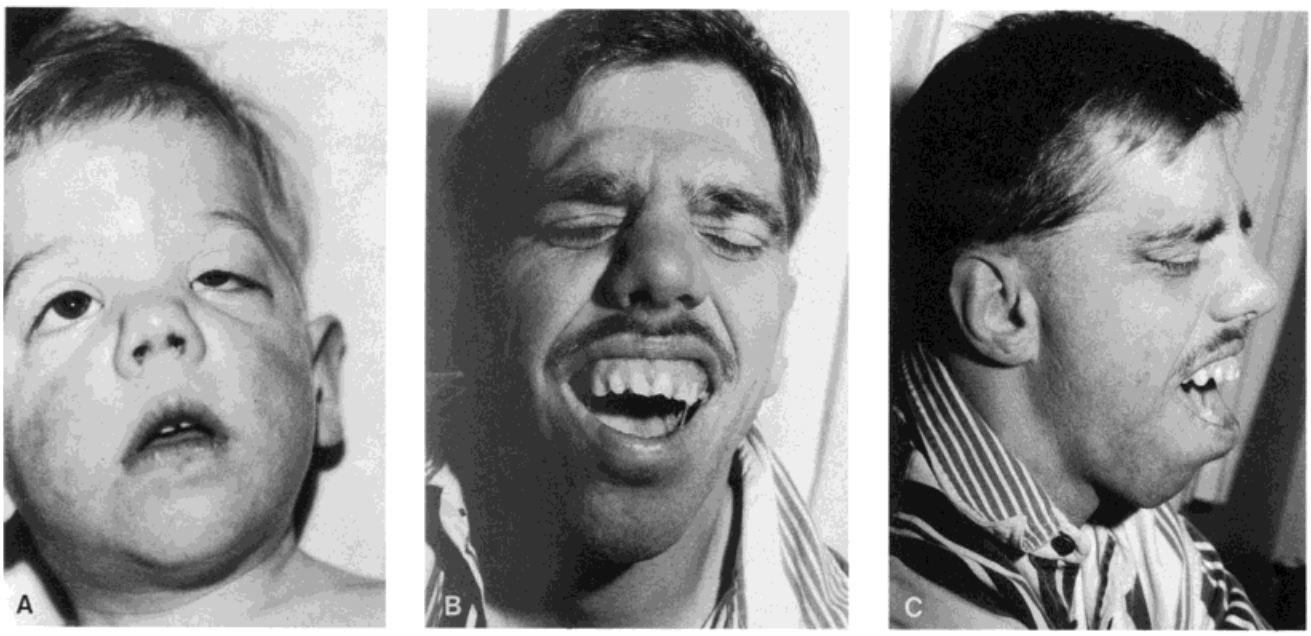

Fig. 1. Facial appearance of "S" at age 10 months (**A**) and at age 33 years (**B** and **C**). A was originally published in Smith et al. [1964], and is reproduced with permission of the publisher.

More importantly, this reassessment has allowed formal documentation of the presence of a cholesterol biosynthetic defect in one of the originally-reported individuals. There is some comfort in confirming the presence of this biochemical abnormality in a defining case and thus confirming the likely identity of Smith-Lemli-Opitz syndrome (as initially defined) and this cholesterol abnormality [Irons et al., 1993, 1994; Tint et al., 1994].

While not rigorously evaluated, it appears that dietary manipulation had a salutary effect on this patient's behavior, despite exceedingly modest changes in plasma cholesterol levels. Diet modification may be of some benefit even in the oldest of individuals with Smith-Lemli-Opitz syndrome, as well as in the very young [Nwokoro et al., 1994]. Similar benefits have been observed previously in adolescents with this disorder [Irons et al., 1995].

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